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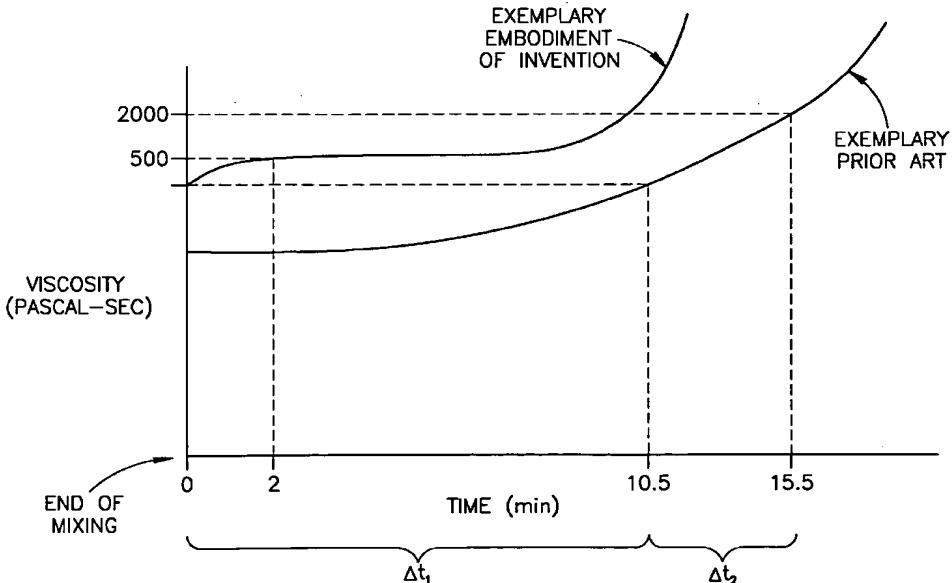
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(54) Title: BONE CEMENT AND METHODS OF USE THEREOF



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(57) Abstract: A bone cement comprising an acrylic polymer mixture. The cement is characterized in that it achieves a viscosity of at least 500 Pascal-second within 180 seconds following initiation of mixing of a monomer component and a polymer component and characterized by sufficient biocompatibility to permit in-vivo use.



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BONE CEMENT AND METHODS OF USE THEREOF**RELATED APPLICATIONS**

The present application claims priority from Israel application No. 174347 filed on March 16, 2006 and entitled "Bone Cement and Methods of Use Thereof" the disclosure of which is incorporated herein by reference.

The present application is a Continuation-in-Part of US application 11/360,251 filed on February 22, 2006, entitled "Methods, Materials and Apparatus for Treating Bone and Other Tissue" and is also a Continuation-in Part of PCT/IL2005/000812 filed on July 31, 2005. The disclosures of these applications are incorporated herein by reference.

10 The present application also claims the benefit under 35 USC 119(e) of a series of US provisional applications entitled "Methods, Materials and Apparatus for Treating Bone and Other Tissue": 60/765,484 filed on February 2, 2006; 60/762,789 filed on January 26, 2006; 60/738,556 filed November 22, 2005; 60/729,505 filed October 25, 2005; 60/720,725 filed on September 28, 2005 and 60/721,094 filed on September 28, 2005. The disclosures of these 15 applications are incorporated herein by reference.

The present application is related to PCT application PCT/IL2006/000239 filed on February 22, 2006; US provisional application 60/763,003, entitled "Cannula" filed on January 26, 2006; US provisional application No. 60/654,495 entitled "Materials, devices and methods for treating bones". filed February 22, 2005; US 11/194,411 filed August 1, 2005; IL 166017 20 filed December 28, 2004; IL 160987 filed March 21, 2004; US Provisional Application No. 60/654,784 filed on January 31, 2005; US Provisional Application No. 60/592,149 filed on July 30, 2004; PCT Application No. PCT/IL2004/000527 filed on June 17, 2004, Israel Application No. 160987 filed on March 21, 2004, U.S. Provisional Applications: 60/478,841 filed on June 17, 2003; 60/529,612 filed on December 16, 2003; 60/534,377 filed on January 6, 25 2004 and 60/554,558 filed on March 18, 2004; U.S. Application No. 09/890,172 filed on July 25, 2001; U.S. Application No. 09/890,318 filed on July 25, 2001 and US application 10/549,409 entitled "Hydraulic Device for the injection of Bone Cement in Percutaneous Vertebroplasty filed on September 14, 2005. The disclosures of all of these applications are incorporated herein by reference.

30 **FIELD OF THE INVENTION**

The present invention relates to bone cement, formulations thereof and methods of use thereof.

BACKGROUND OF THE INVENTION

It is common to employ cement to repair bones in a variety of clinical scenarios.

For example, compression fractures of the vertebrae, which are a common occurrence in older persons, cause pain and/or a shortening (or other distortion) of stature. In a procedure known as vertebroplasty cement is injected into a fractured vertebra. Vertebroplasty stabilizes the fracture and reduces pain, although it does not restore the vertebra and person to their original height. In vertebroplasty the cement is typically injected in a liquid phase so that resistance to injection is not too great. Liquid cement may unintentionally be injected outside of the vertebra and/or may migrate out through cracks in the vertebra.

In another procedure, known as kyphoplasty, the fracture is reduced by expanding a device, such as a balloon inside the vertebra and then injecting a fixing material and/or an implant. Kyphoplasty reduces the problem of cement leakage by permitting a lower pressure to be used for injection of the cement.

In general, polymeric cements become more viscous as the polymer chain grows by reacting directly with the double bond of a monomer. Polymerization begins by the "addition mechanism" in which a monomer becomes unstable by reacting with an initiator, a volatile molecule that is most commonly a radical (molecules that contain a single unpaired electron). Radicals bond with monomers, forming monomer radicals that can attack the double bond of the next monomer to propagate the polymer chain. Because radicals are so transient, initiators are often added in the form of an un-reactive peroxide form which is stable in solution. Radicals are formed when heat or light cleaves the peroxide molecule. For applications in which high temperatures are not practical (such as the use of bone cement *in vivo*), peroxide is typically cleaved by adding a chemical activator such as N, N-dimethyl-p-toluidine. (Nussbaum DA et al: "The Chemistry of Acrylic Bone Cement and Implication for Clinical Use in Image-guided Therapy", J Vasc Interv Radiol (2004); 15:121-126; the content of which is fully incorporated herein by reference).

Examples of commercially available viscous bone cements include, but are not limited to, CMW® Nos. 1, 2 and 3 (DePuy Orthopaedics Inc.; Warsaw, IN, USA) and Simplex™ -P and -RO (Stryker Orthopaedics; Mahwah, NJ, USA). These cements are characterized by a liquid phase after mixing and prior to achieving a viscosity of 500 Pascal-second. In a typical use scenario, these previously available cements are poured, while in a liquid phase, into a delivery device.

There have also been attempts to reduce cement leakage by injecting more viscous cement, for example, during the doughing time and the beginning of polymerization. However, the viscous materials, such as hardening PMMA, typically harden very quickly once they reach

a high viscosity. This has generally prevented injection of viscous materials in orthopedic procedures.

Some bone fixing materials, such as polymethylmethacrylate (PMMA), emit heat and possibly toxic materials while setting.

5 US patents and publication 4,969,888, 5,108,404, 6,383,188, 2003/0109883, 2002/0068974, 6,348,055, 6,383,190, 4,494,535, 4,653,489 and 4,653,487, the disclosures of which are incorporated herein by reference describe various tools and methods for treating bone.

10 US patent publication 2004/0260303, the disclosure of which is incorporated herein by reference, teaches an apparatus for delivering bone cement into a vertebra.

Pascual, B., et al., "New Aspects of the Effect of Size and Size Distribution on the Setting Parameters and Mechanical Properties of Acrylic Bone Cements," *Biomaterials*, 17(5): 509-516 (1996) considers the effect of PMMA bead size on setting parameters of cement. This article is fully incorporated herein by reference.

15 Hernandez, et al., (2005) "Influence of Powder Particle Size Distribution on Complex Viscosity and Other Properties of Acrylic Bone Cement for Vertebroplasty and Kyphoplasty" Wiley International Science D01:10:1002/jbm.b.30409 (pages 98-103) considers the effect of PMMA bead size distribution on setting parameters of cement. Hernandez suggests that it is advantageous to formulate cement with a liquid phase to facilitate injection. This article is fully 20 incorporated herein by reference.

US 5,276,070 to Arroyo discloses use of acrylic polymers with a molecular weight in the range of 0.5 to 1.5 million Daltons in formulation of bone cement. The disclosure of this patent is fully incorporated herein by reference.

25 US 5,336,699 to Cooke discloses use of acrylic polymers with a molecular weight of about one hundred thousand Daltons in formulation of bone cement. The disclosure of this patent is fully incorporated herein by reference.

SUMMARY OF THE INVENTION

A broad aspect of the invention relates to a bone cement characterized by a rapid transition from separate liquid monomer and powdered polymer components to a single phase 30 characterized by a high viscosity when the components are mixed together with substantially no intervening liquid phase. Optionally, high viscosity indicates 500 Pascal-second or more. Mixing is deemed complete when 95-100% of the polymer beads are wetted by monomer. In an exemplary embodiment of the invention, mixing is complete in within 60, optionally within 45, optionally within 30 seconds.

In an exemplary embodiment of the invention, the cement is characterized by a working window of several minutes during which the viscosity remains high prior to hardening of the cement. Optionally, viscosity during the working window does not vary to a degree which significantly influences injection parameters. In an exemplary embodiment of the invention, 5 viscosity increases by less than 10% during a sub-window of at least 2 minutes during the working window. Optionally, the viscosity in the working window does not exceed 500, optionally 1,000, optionally 1,500, optionally 2,000 Pascal-second or lesser or greater or intermediate values. In an exemplary embodiment of the invention, the working window lasts 6, optionally 8, optionally 10, optionally 15 minutes or lesser or greater or intermediate times. 10 Optionally, ambient temperature influences a duration of the working window. In an exemplary embodiment of the invention, the cement can be cooled or heated to influence a length of the working window.

An aspect of some embodiments of the invention relates to formulations of bone cement which rely upon two, optionally three or more, sub-populations of polymer beads 15 which are mixed with liquid monomer.

According to exemplary embodiments of the invention, sub-populations may be characterized by average molecular weight (MW) and/or physical size and/or geometry, and/or density. In an exemplary embodiment of the invention, size based and MW based sub-populations are defined independently. In an exemplary embodiment of the invention, the sub- 20 populations are selected to produce desired viscosity characterization and/or polymerization kinetics. Optionally, the polymer beads comprise polymethylmethacrylate (PMMA) and/or a PMMA or MMA styrene copolymer. Optionally, PMMA is employed in conjunction with a methylmethacrylate (MMA) monomer.

Optionally, a high molecular weight sub-population contributes to a rapid transition to a 25 high viscosity with substantially no liquid phase. Optionally, a low molecular weight subpopulation contributes to a longer working window.

Optionally, a sub-population with small size contributes to rapid wetting of polymer beads with monomer solution. In an exemplary embodiment of the invention, rapid wetting contributes to a direct transition to a viscous cement with substantially no liquid phase.

30 In some cases a small percentage of beads may not belong to any relevant sub-population. The small percentage may be, for example 1%, 1.5%, 2%, 3%, 4%, 5% or lesser or intermediate or greater percentages.

In one exemplary embodiment of the invention, there are at least two sub-populations of PMMA polymer beads characterized by molecular weights. For example, a first sub-

population comprising 95 to 97% (w/w) of the total PMMA beads can be characterized by an average MW of 270,000-300,000 Dalton; a second sub-population (2-3% w/w) can be characterized by an average MW of 3,500,000-4,000,000 Dalton; and a third sub-population (0-3% w/w) can be characterized by an average MW of 10,000-15,000 Dalton.

5 In an exemplary embodiment of the invention, the polymer beads are characterized by a high surface area per unit weight. Optionally, the beads have a surface area of 0.5 to 1, optionally 0.5 to 0.8 optionally about 0.66 m²/gram or intermediate or lesser or greater values. Optionally, the high surface area/weight ratio improves wetting properties and/or shortens polymerization times, for example by contributing to polymer monomer contact.

10 In an exemplary embodiment of the invention, a cement characterized by an immediate transition to high viscosity is injected during a working window in a vertebroplasty or kyphoplasty procedure. Optionally, injection is under sufficient pressure to move fractured bone, such as vertebral plates of a collapsed vertebra. Optionally, injection of viscous cement under high pressure contributes to fracture reduction and/or restoration of vertebral height.

15 In an exemplary embodiment of the invention, the material (e.g., bone cement) includes processed bone (from human or animals origin) and/or synthetic bone. Optionally, the cement has osteoconductive and/or osteoinductive behavior. Additional additives as commonly used in bone cement preparation may optionally be added. These additives include, but are not limited to, barium sulfate and benzoyl peroxide.

20 According to some embodiments of the invention, a working window length is determined by an interaction between an immediate effect and a late effect. In an exemplary embodiment of the invention, the immediate effect includes MMA solvation and/or encapsulation of PMMA polymer beads. The immediate effect contributes to a high viscosity of the initial mixture resulting from solvation and/or friction between the beads. The late effect 25 is increasing average polymer MW as the beads dissolve and the polymerization reaction proceeds. This increasing average polymer MW keeps viscosity high throughout the working window.

In an exemplary embodiment of the invention, a set of viscosity parameters are used to adjust a cement formulation to produce a cement characterized by a desired working window at 30 a desired viscosity.

In an exemplary embodiment of the invention, there is provided a bone cement comprising an acrylic polymer mixture, the cement characterized in that it achieves a viscosity of at least 500 Pascal-second within 180 seconds following initiation of mixing of a monomer

component and a polymer component and characterized by sufficient biocompatibility to permit in-vivo use.

Optionally, the viscosity of the mixture remains between 500 and 2000 Pascal-second for a working window of at least 5 minutes after the initial period.

5 Optionally, the working window is at least 8 minutes long.

 Optionally, the mixture includes PMMA.

 Optionally, the mixture includes Barium Sulfate.

 Optionally, the PMMA is provided as a PMMA/styrene copolymer.

 Optionally, the PMMA is provided as a population of beads divided into at least two
10 sub-populations, each sub-population characterized by an average molecular weight.

 Optionally, a largest sub-population of PMMA beads is characterized by an MW of
150,000 Dalton to 300,000 Dalton.

 Optionally, a largest sub-population of PMMA beads includes 90-98% (w/w) of the
beads.

15 Optionally, a high molecular weight sub-population of PMMA beads is characterized
by an average MW of at least 3,000,000 Dalton.

 Optionally, a high molecular weight sub-population of PMMA beads includes 2 to 3%
(w/w) of the beads.

20 Optionally, a low molecular weight sub-population of PMMA beads is characterized by
an average MW of less than 15,000 Dalton.

 Optionally, a low molecular weight sub-population of PMMA beads includes 0.75 to
1.5 % (W/W) of the beads.

 Optionally, the PMMA is provided as a population of beads divided into at least two
sub-populations, each sub-population characterized by an average bead diameter.

25 Optionally, at least one bead sub-population characterized by an average diameter is
further divided into at least two sub-sub-populations, each sub-sub-population characterized by
an average molecular weight.

 Optionally, the PMMA is provided as a population of beads divided into at least three
sub-populations, each sub-population characterized by an average bead diameter.

30 Optionally, the cement further includes processed bone and/or synthetic bone.

 Optionally, the cement is characterized in that the cement achieves a viscosity of at
least 500 Pascal-second when 100% of a polymer component is wetted by a monomer
component.

 Optionally, the viscosity is at least 800 Pascal-second.

Optionally, the viscosity is at least 1500 Pascal-second.

Optionally, the viscosity is achieved within 2 minutes.

Optionally, the viscosity is achieved within 1 minute.

Optionally, the viscosity is achieved within 45 seconds.

5 In an exemplary embodiment of the invention, there is provided a bone cement comprising:

a polymer component; and

a monomer component,

wherein, contacting the polymer component and the monomer component produces a
10 mixture which attains a viscosity greater than 200 Pascal-second within 1 minute from onset of mixing and remains below 2000 Pascal-second until at least 6 minutes from onset of mixing.

Optionally, the polymer component comprises an acrylic polymer.

In an exemplary embodiment of the invention, there is provided a particulate mixture formulated for preparation of a bone cement, the mixture comprising:

15 (a) 60 to 80% polymer beads comprising a main sub-population characterized by an MW of 150,000 Dalton to 300,000 Dalton and a high molecular weight sub-population characterized by an MW of 3,000,000 Dalton to 4,000,000 Dalton; and

(b) 20 to 40% of a material which is non-transparent with respect to X-ray.

Optionally, the polymer beads comprise a third subpopulation characterized by an MW
20 of 10,000 Dalton to 15,000 Dalton.

In an exemplary embodiment of the invention, there is provided a method of making a polymeric bone cement, the method comprising:

(a) defining a viscosity profile including a rapid transition to a working window characterized by a high viscosity;

25 (b) selecting a polymer component and a monomer component to produce a cement conforming to the viscosity profile; and

(c) mixing the polymer component and a monomer component to produce a cement which conforms to the viscosity profile.

30 **BRIEF DESCRIPTION OF THE FIGURES**

Exemplary non-limiting embodiments of the invention will be described with reference to the following description of embodiments in conjunction with the figures. Identical structures, elements or parts which appear in more than one figure are generally labeled with a same or similar number in all the figures in which they appear, in which:

Fig. 1 is a flow diagram illustrating an exemplary method 100 of preparation and behavior of exemplary cements according to the present invention;

Fig. 2 is a graph of viscosity profiles depicting viscosity (Pascal-second) as a function of time (minutes) for an exemplary cement according to the invention and an exemplary prior art cement; and

Figs. 3 and 4 are graphs indicating viscosity as Newtons of applied force per unit displacement (mm) under defined conditions for exemplary cements according to the invention and illustrate the time window for injection which is both early and long.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

10 Overview of preparation of exemplary bone cement

Fig. 1 is a flow diagram illustrating preparation and behavior of exemplary cements according to some embodiments of the present invention.

In an exemplary embodiment of the invention, a liquid monomer and a powdered polymer component of a bone cement are combined 110. Optionally, liquid monomer is poured onto powdered polymer.

According to various embodiments of the invention, average polymer molecular weight and/or polymer molecular weight distribution and/or polymer bead size is precisely controlled in order to influence polymerization kinetics and/or cement viscosity. Alternatively or additionally, polymer and/or monomer components may contain ingredients which are not directly involved in the polymerization reaction.

In an exemplary embodiment of the invention, the polymer (e.g. an acrylic polymer such as PMMA) beads are divided into two or more sub-populations. Optionally, the sub-populations are defined by molecular weight (MW). In an exemplary embodiment of the invention, the average molecular weight of the acrylic polymer in all the beads is in the range of about 300,000 to 400,000, optionally about 373,000 Dalton. This average MW for all beads was determined experimentally for a batch of beads which produced cement with a desired polymerization profile.

Optionally, the polymer beads are provided as part of an acvrylic polymer mixture, for example a mixture including barium sulfate.

At 112 the components are mixed until the polymer is wetted by the monomer. Optionally, when wetting is 95 to 100% complete, the mixture has achieved a desired high viscosity, for example 500 Pascal-second or more. Optionally, mixing 112 is complete within 1, 5, 10, 15, 30, 60, 90, 120 or 180 seconds. In a modern medical facility, it can be advantageous to shorten the mixing time in order to reduce the demand on physical facilities

and/or medical personnel. A savings of even 1 to 2 minutes with respect to previously available alternatives can be significant. In an exemplary embodiment of the invention, mixing 112 is conducted in a mixing apparatus of the type described in co-pending application US 11/428,908, the disclosure of which is fully incorporate herein by reference.

5 After mixing 112 is complete, a working window 114 during which the cement remains viscous but has not fully hardened occurs. According to various exemplary embodiments of the invention, working window 114 may be about 2, 5, 8, 10, 15 or 20 minutes or intermediate or greater times. The duration of the working window may vary with the exact cement formulation and/or ambient conditions (e.g. temperature and/or humidity). Formulation 10 considerations include, but are not limited to polymer MW (average and/or distribution), polymer bead size, concentrations of non-polymerizing ingredient and polymer: monomer ratio.

15 Working window 114, permits a medical practitioner sufficient time to load a high pressure injection device and inject 120 the cement into a desired location. Optionally, an injection needle or cannula is inserted into the body prior to, or concurrent with mixing 112 so that window 114 need only be long enough for loading and injection 120. Exemplary injection systems are disclosed in co-pending application US 11/360,251 entitled "Methods, materials, and apparatus for treating bone and other tissue" filed February 22, 2006, the disclosure of which is fully incorporated herein by reference.

20 In an exemplary embodiment of the invention, hardening 116 to a hardened condition occurs after working window 114. The cement hardens 116 even if it has not been injected.

Advantages with Respect to Relevant Medical Procedures

25 In an exemplary embodiment of the invention, cement with a viscosity profile as described above is useful in vertebral repair, for example in vertebroplasty and/or kyphoplasty procedures.

30 Optionally, use of cement which is viscous at the time of injection reduces the risk of material leakage and/or infiltrates into the intravertebral cancellous bone (interdigitaion) and/or reduces the fracture [see G Baroud *et al*, Injection biomechanics of bone cements used in vertebroplasty, Bio-Medical Materials and Engineering 00 (2004) 1-18]. Reduced leakage optionally contributes to increased likelihood of a positive clinical outcome.

In an exemplary embodiment of the invention, the viscosity of the bone cement is 500, optionally 1,000, optionally 1,500, optionally 2,000 Pascal-second or lesser or greater or intermediate values at the time injection begins, optionally 3, 2 or 1 minutes or lesser or intermediate times after mixing 112 begins. Optionally, the viscosity does not exceed 2,000

Pascal-second during working window 114. In an exemplary embodiment of the invention, this viscosity is achieved substantially as soon as 95-100% of the polymer beads are wetted by monomer.

5 Cement characterized by a high viscosity as described above may optionally be manually manipulated.

In an exemplary embodiment of the invention, cement is sufficiently viscous to move surrounding tissue as it is injected. Optionally, moving of the surrounding tissue contributes to fracture reduction and/or restoration of vertebral height.

An injected volume of cement may vary, depending upon the type and/or number of 10 orthopedic procedures being performed. The volume injected may be, for example, 2-5 cc for a typical vertebral repair and as high as 8-12 cc or higher for repairs of other types of bones. Other volumes may be appropriate, depending for example, on the volume of space and the desired effect of the injection. In some cases, a large volume of viscous cement is loaded into a delivery device and several vertebrae are repaired in a single medical procedure. Optionally, 15 one or more cannulae or needles are employed to perform multiple procedures.

Viscous cements according to exemplary embodiments of the invention may be delivered at a desired flow rate through standard orthopedic cannulae by applying sufficient pressure. Exemplary average injection rates may be in the range of 0.01 to 0.5 ml/sec, 20 optionally about 0.05, about 0.075 or 0.1 ml/sec or lesser or intermediate or greater average flow rates. Optionally, the flow rate varies significantly during an injection period (e.g., pulse injections). Optionally, the flow rate is controlled manually or using electronic or mechanical circuitry. In an exemplary embodiment of the invention, medical personnel view the cement as 25 it is being injected (e.g. via fluoroscopy) and adjust a flow rate and/or delivery volume based upon observed results. Optionally, the flow rate is adjusted and/or controlled to allow a medical practitioner to evaluate progress of the procedure based upon medical images (e.g. fluoroscopy) acquired during the procedure. In an exemplary embodiment of the invention, the cement is sufficiently viscous that advances into the body when pressure is applied above a threshold and ceases to advance when pressure is reduced below a threshold. Optionally, the threshold varies with one or more of cement viscosity, cannula diameter and cannula length.

30 **Comparison of exemplary formulations according to some embodiments of the invention to previously available formulations**

Although PMMA has been widely used in preparation of bone cement, previously available PMMA based cements were typically characterized by a persistent liquid state after mixing of components.

In sharp contrast, cements according to some exemplary embodiments of the invention are characterized by essentially no liquid state. Optionally, a direct transition from separate polymer and monomer components to a highly viscous state results from the presence of two or more sub-populations of polymer beads.

5 As a result of formulations based upon bead sub-populations, a viscosity profile of a cement according to an exemplary embodiment of the invention is significantly different from a viscosity profile of a previously available polymer based cement (e.g. PMMA) with a similar average molecular.

Because the viscosity profile of previously available PMMA cements is typically
10 characterized by a rapid transition from high viscosity to fully hardened, these cements are typically injected into bone in a liquid phase so that they do not harden during injection.

In sharp contrast, exemplary cements according to the invention remain highly viscous during a long working window 114 before they harden. This long working window permits performance of a medical procedure of several minutes duration and imparts the advantages of
15 the high viscosity material to the procedure.

It should be noted that while specific examples are described, it is often the case that the formulation will be varied to achieve particular desired mechanical properties. For example, different diagnoses may suggest different material viscosities which may, in turn lead to adjustment of one or more of MW (average and/or distribution), bead size and bead surface
20 area.

In an exemplary embodiment of the invention, the cement is mixed 112 and reaches high viscosity outside the body. Optionally the materials are mixed under vacuum or ventilated. In this manner, some materials with potentially hazardous by-products can be safely mixed and then used in the body.

25 In an exemplary embodiment of the invention, the cement is formulated so that its mechanical properties match the bone in which it will be injected/implanted. In an exemplary embodiment of the invention, the cement is formulated to mechanically match healthy or osteoporotic trabecular (cancellous) bone. Optionally, the mechanical properties of the bone are measured during access, for example, based on a resistance to advance or using sensors
30 provided through a cannula or by taking samples, or based on x-ray densitometry measurements. In an exemplary embodiment of the invention, strength of the cement varies as a function of one or more of a size of the high MW sub-population and/or a relationship between bead size and bead MW.

In general, PMMA is stronger and has a higher Young modulus than trabecular bone. For example, healthy Trabecular bone can have a strength of between 1.5-8.0 mega Pascal and a Young modulus of 60-500 mega Pascal. Cortical bone, for example, has strength values of 65-160 mega Pascal and Young modulus of 12-40 giga Pascal. PMMA typically has values 5 about half of Cortical bone (70-120 mega Pascal strength).

Fig. 2 is a plot of viscosity as a function of time for an exemplary bone cement according to the present invention. The figure is not drawn to scale and is provided to illustrate the principles of exemplary embodiments of the invention. The end of a mixing process is denoted as time 0. Mixing is deemed to end when 95-100% of acrylic polymer beads have been 10 wetted with monomer. The graph illustrates an exemplary bone cement which enters a high viscosity plastic phase upon mixing so that it has substantially no liquid phase.

Fig. 2 illustrates that once a high viscosity is achieved, the viscosity remains relatively stable for 2, optionally 5, optionally 8 minutes or more. In an exemplary embodiment of the invention, this interval of stable viscosity provides a working window 114 (indicated here as 15 Δt_1) for performance of a medical procedure. In an exemplary embodiment of the invention, stable viscosity means that the viscosity of the cement changes by less than 200 Pascal-second during a window of at least 2 minutes optionally at least 4 minutes after mixing is complete. Optionally, the window begins 1, 2, 3, 4 or 5 minutes after mixing begins or lesser or intermediate times. In an exemplary embodiment of the invention, the viscosity of the cement 20 remains below 1500, optionally 2000 Pascal-second for at least 4, optionally at least 6, optionally at least 8, optionally at least 10 minutes or intermediate or greater times from onset of mixing.

For purposes of comparison, the graph illustrates that an exemplary prior art cement reaches a viscosity comparable to that achieved by an exemplary cement according to the 25 invention at time zero at a time of approximately 10.5 minutes post mixing and is completely set by about 15.5 minutes (Δt_2).

A working window 114 during which viscosity is between 400 and 2000 Pascal-second for an exemplary cement according to some embodiments of the invention (Δt_1) is both longer and earlier than a comparable window for an exemplary prior art cement (Δt_2). Optionally, 30 (Δt_1) begins substantially as soon as mixing is complete.

Exemplary cement formulations

According to various exemplary embodiments of the invention, changes in the ratios between a powdered polymer component and a liquid monomer component can effect the

duration of working window 114 and/or a viscosity of the cement during that window. Optionally, these ratios are adjusted to achieve desired results.

In an exemplary embodiment of the invention, the powdered polymer component contains PMMA (69.3% w/w); Barium sulfate (30.07% w/w) and Benzoyl peroxide (0.54% w/w).

In an exemplary embodiment of the invention, the liquid monomer component contains MMA (98.5% v/v); N, N-dimethyl-p-toluidine (DMPT) (1.5% v/v) and Hydroquinone (20 ppm).

In a first exemplary embodiment of the invention, 20 ± 0.3 grams of polymer powder and 9 ± 0.3 grams of liquid monomer are combined (weight ratio of ~2.2:1).

In a second exemplary embodiment of the invention, 20 ± 0.3 grams of polymer powder and 8 ± 0.3 grams of liquid are combined (weight ratio of 2.5:1).

Under same weight ratio of second exemplary embodiment (2.5:1), a third exemplary embodiment may include a combination of 22.5 ± 0.3 grams of polymer powder and 9 ± 0.3 grams of liquid.

In general, increasing the weight ratio of polymer to monomer produces a cement which reaches a higher viscosity in less time. However, there is a limit beyond which there is not sufficient monomer to wet all of the polymer beads.

Optionally the powdered polymer component may vary in composition and contain PMMA (67-77%, optionally 67.5-71.5% w/w); Barium sulfate (25-35%; optionally 28-32% w/w) and Benzoyl peroxide (0.4 -0.6 % w/w) and still behave substantially as the powder component recipe set forth above. .

Optionally the liquid monomer component may vary in composition and contain Hydroquinone (1-30 ppm; optionally 20-25 ppm) and still behave substantially as the liquid component recipe set forth above. .

Viscosity measurements over time for exemplary cements

In order to evaluate the viscosity profile of different exemplary batches of cement according to some embodiments of the invention, a bulk of pre-mixed bone cement is placed inside a Stainless Steel injector body. Krause et al. described a method for calculating viscosity in terms of applied force. ("The viscosity of acrylic bone cements", Journal of Biomedical Materials Research, (1982): 16:219-243). This article is fully incorporated herein by reference.

In the experimental apparatus an inner diameter of the injector body is approximately 18 mm. A distal cylindrical outlet has an inner diameter of approximately 3 mm and a length of more than 4 mm. This configuration simulates a connection to standard bone cement delivery

cannula/bone access needle. A piston applies force (F), thus causing the bone cement to flow through the outlet. The piston is set to move with constant velocity of approximately 3 mm/min. As a result, piston deflection is indicative of elapsed time.

The experimental procedure serves as a kind of capillary extrusion rheometer. The 5 rheometer measures the pressure difference from an end to end of the capillary tube. The device is made of an 18 mm cylindrical reservoir and a piston. The distal end of the reservoir consist of 4 mm long 3 mm diameter hole. This procedure employs a small diameter needle and high pressure. Assuming steady flow, isothermal conditions and incompressibility of the tested material, the viscous force resisting the motion of the fluid in the capillary is equal to the 10 applied force acting on the piston measured by a load cell and friction. Results are presented as force vs. displacement. As displacement rate was constant and set to 3 mm/min, the shear rate was constant as well. In order to measure the time elapses from test beginning, the displacement rate is divided by 3 (jog speed).

Fig. 3 indicates a viscosity profile of a first exemplary batch of cement according to the 15 invention as force (Newtons) vs. displacement (mm). The cement used in this experiment included a liquid component and a powder component as described above in "Exemplary cement formulations".

In this test (Average temperature: 22.3°C; Relative Humidity: app. 48%) the cement was mixed for 30-60 seconds, then manipulated by hand and placed inside the injector. Force 20 was applied via the piston approximately 150 seconds after end of mixing, and measurements of force and piston deflection were taken.

At a time of 2.5 minutes after mixing (0 mm deflection) the force applied was higher than 30 N.

At a time of 6.5 minutes after mixing (12 mm deflection) the force applied was about 25 150 N.

At a time of 7.5 minutes after mixing (15 mm deflection) the force applied was higher than 200 N.

At a time of 8.5 minutes after mixing (18 mm deflection) the force applied was higher than 500 N.

30 At a time of 9.17 minutes after mixing (20 mm deflection) the force applied was higher than 1300 N.

Fig. 4 indicates a viscosity profile of an additional exemplary batch of cement according to the invention as force (Newtons) vs. displacement (mm). The cement in this test was prepared according to the same formula described for the experiment of Fig. 3. In this test

(Average 21.1°C; Relative Humidity: app. 43%) the cement was mixed for approximately 45 seconds, then manipulated by hand and placed inside the injector. Force was applied via piston approximately 150 seconds after end of mixing, and measurements of force and piston deflection were taken.

5 At a time of 2.25 minutes after mixing (0 mm deflection) the force applied was higher than 30 N.

At a time of 8.25 minutes after mixing (18 mm deflection) the force applied was about 90 N.

10 At a time of 10.3 minutes after mixing (25 mm deflection) the force applied was higher than 150 N.

At a time of 11.4 minutes after mixing (28.5 mm deflection) the force applied was higher than 500 N.

At a time of 12.25 minutes after mixing (30 mm deflection) the force applied was higher than 800 N.

15 Results shown in Figs. 3 and 4 and summarized hereinabove illustrate that exemplary bone cements according to some embodiments the invention achieve high viscosity in 2.25 minutes or less after mixing is completed. Alternatively or additionally, these cements are characterized by short mixing time (i.e. transition to highly viscous plastic phase in 30 to 60 seconds). The exemplary cements provide a “working window” for injection of 4.5 to 6.3 minutes, optionally longer if more pressure is applied and/or ambient temperatures are lower. These times correspond to delivery volumes of 14.9 and 20.8 ml respectively (vertebroplasty of a single vertebra typically requires about 5 ml of cement). These volumes are sufficient for most vertebral repair procedures. These results comply with the desired characteristics described in Fig. 2. Differences between the two experiments may reflect the influence of 20 temperature and humidity on reaction kinetics.

25

Molecular weight distribution

In an exemplary embodiment of the invention, the average molecular weight (MW) is skewed by the presence of one or more small sub-population of beads with a molecular weight which is significantly different from a main sub-population of polymer beads. The one or more 30 small sub-population of beads may have a MW which is significantly higher and/or significantly lower than the average MW.

In an exemplary embodiment of the invention, the presence of even a relatively small sub-population of polymer beads with a MW significantly above the average MW causes the cement to achieve a high viscosity in a short time after wetting of polymer beads with

monomer solution. Optionally, increasing a size of the high MW sub-population increases the achieved viscosity. Alternatively or additionally, increasing an average MW of the high MW sub-population increases the achieved viscosity and/or decreases the time to reach high viscosity.

5 Optionally, the one or more small sub-population of beads are provided in a formulation in which, the average molecular weight of PMMA in all beads is 80,000, optionally 100,000, optionally 120,000, optionally 140,000, optionally 160,000, optionally 180,000, optionally, 250,000, optionally 325,000, optionally 375,000, optionally 400,000, optionally 500,000 Dalton or intermediate or lesser or greater values.

10 In another exemplary embodiment of the invention, the average molecular weight of the acrylic polymer in the beads is in the range of about 130,000 to 170,000, optionally about 160,000 Dalton.

15 In an exemplary embodiment of the invention, a main sub-population of PMMA beads has a MW of about 150,000 Dalton to about 500,000 Dalton, optionally about 250,000 Dalton to about 300,000 Dalton, optionally about 275,000 Dalton to about 280,000 Dalton. Optionally, about 90-98% [w/w], optionally about 93% to 98%, optionally about 95% to 97% of the beads belong to the main sub-population.

20 In an exemplary embodiment of the invention, a second high MW sub-population of PMMA beads has a MW of about 600,000 Dalton, to about 5,000,000 Dalton, optionally about 3,000,000 Dalton to about 4,000,000 Dalton, Optionally about 3,500,000 Dalton to about 3,900,000 Dalton. Optionally, approximately 0.25% to 5% [w/w], optionally about 1% to 4%, optionally about 2% to 3% of the beads belong to this high MW sub-population. Optionally, this high molecular weight sub-population comprises a styrene co-polymer. In an exemplary embodiment of the invention, a higher molecular weight in this sub-population of beads contributes to a high viscosity within 2, optionally within 1, optionally within 0.5 minutes or less of wetting of polymer beads with monomer solution.

25 In an exemplary embodiment of the invention, a third low MW sub-population of PMMA beads has a MW in the range of about 1,000 Dalton to about 75,000 Dalton, optionally about 10,000 Dalton to about 15,000 Dalton, optionally about 11,000 Dalton to about 13,000 Dalton. Optionally, approximately 0.5 to 2.0% [w/w], optionally about 1% of the beads belong to this sub-population.

30 Optionally the MW sub-populations are distinct from one another. This can cause gaps between sub-populations with respect to one or more parameters. In an exemplary embodiment of the invention, the sub-populations are represented as distinct peaks in a chromatographic

separation process. Optionally, the peaks are separated by a return to baseline. Depending upon the sensitivity of detection, a background level of noise may be present. Optionally, gaps are measured relative to the noise level.

5 Optionally the sub-populations abut one another so that no gaps are apparent. In an exemplary embodiment of the invention, the sub-populations are represented as overlapping peaks in a chromatographic separation process. In this case, there is no return to baseline between the peaks.

Experimental analysis of an exemplary batch of cement

10 Sub-populations characterized by an average molecular weight were identified and quantitated using chromatographic techniques known in the art. Exemplary results described herein are based upon GPC analysis. Each peak in the GPC analysis is considered a sub-population. Similar analyses may be conducted using HPLC. Results are summarized in table 1.

15 **Table I: MW distribution of polymer beads based upon GPC analysis of a bone cement according to the powdered polymer component described in “Exemplary cement formulations” hereinabove.**

Fraction	% of total	PDI ¹	Mw ²	Mn ³
1	96.5	1.957	278,986	142,547
2	2.5	1.048	3,781,414	3,608,941
3	1.0	1.009	12,357	12,245
	100.0	2.955	373,046	126,248

1 1 polydispersity index (PDI), is a measure of the distribution of molecular weights in a given polymer sample and is equal to MW/Mn.

2 2 MW is the weight average molecular weight in Daltons

3 3 Mn is the number average molecular weight in Daltons

20

Table I illustrates an exemplary embodiment of the invention with three sub-populations of acrylic polymer beads.

The main sub-population (fraction 1) of PMMA beads has a molecular weight (MW) of 278,986 Dalton. About 96.5% of the beads belong to this sub-population.

25

A second sub-population (fraction 2) of PMMA beads has MW of 3,781,414 Dalton. Approximately 2.5% of the beads belong to this sub-population.

A third sub-population of PMMA beads (fraction 3) has an MW of 12,357 Dalton. Approximately 1% of the beads belong to this sub-population.

30

In an exemplary embodiment of the invention, cement comprising these three sub-populations is characterized by a short mixing time and/or achieves a viscosity of 500 to 900 Pascal-second in 0.5 to 3, optionally 0.5 to 1.5 minutes from the beginning of mixing and/or which remains below 2000 Pascal-second for at least 6 to 10 minutes after mixing. A short

mixing time followed by a long working window is considered advantageous in orthopedic procedures where operating room availability and medical staff are at a premium.

Size Distribution

In an exemplary embodiment of the invention, the bone cement is characterized by 5 beads with a size distribution including at least two sub-populations of polymer beads.

In an exemplary embodiment of the invention, polymer bead diameter is in the range of 10-250 microns, with a mean value of approximately 25, 30, 40, 50, 60 microns, or a lower or a higher or an intermediate diameter. In an exemplary embodiment of the invention, sub-populations of beads are defined by their size.

10 Optionally, a main sub-population of polymer (e.g. PMMA) beads is characterized by a diameter of about 20 to about 150, optionally about 25 to about 35, optionally an average of about 30 microns. Beads in this main sub-population are optionally far smaller than the smallest beads employed by Hernandez et al. (2005; as cited above). Presence of small beads can contribute to a rapid increase in viscosity after wetting with monomer.

15 Optionally a second sub-population of large polymer beads is characterized by a diameter of about 150 microns or more. Presence of large beads can slow down the polymerization reaction and prevent hardening, contributing to a long working window.

20 Optionally, the remaining beads are characterized by a very small average diameter, for example less than 20, optionally less than 15, optionally about 10 microns or less. Presence of very small beads can facilitate rapid wetting with monomer liquid during mixing and contribute to a fast transition to a viscous state with substantially no liquid phase.

Microscopic analysis indicates that the beads are typically spherical or spheroid.

Hernandez et al. (2005; as cited above) examined the possibility of adjusting the 25 average polymer bead size by combining two types of beads with average sizes of 118.4 μ (Colacry) and 69.7 μ (Plexigum) together in different ratios. However, Hernandez's goal was a formulation which is "liquid enough to be injected". All formulations described by Hernandez are characterized by an increase in viscosity from 500 Pascal-sec to 2000 Pascal-sec in about two minutes or less (corresponds to window 114). Hernandez does not hint or suggest that there is any necessity or advantage to increasing the size of this window.

30 Microscopic analysis also indicated that the barium sulfate particles are present as elongate amorphous masses with a length of approximately 1 micron. In some cases aggregates of up to 70 microns in size were observed. In some cases, barium sulfate particles and polymer beads aggregated together. Optionally, aggregates of Barium sulfate and polymer beads can delay wetting of polymer beads by monomer.

In an exemplary embodiment of the invention, MMA solvates and/or encapsulates the PMMA polymer beads and the viscosity of the initial mixture is high due to the solvation and/or friction between the beads. As the beads dissolve viscosity remains high due to polymerization which increases the average polymer MW.

5 Size and MW are independent variables

In an exemplary embodiment of the invention, size based and MW based sub-populations are determined independently. For example, MW may be determined chromatographically and size may be determined by microscopic analysis. As a result, beads classed in a single size sub-population may be classed in two or more MW sub-populations 10 and/or beads classed in a single MW sub-population may be classed in two or more size sub-populations.

Mechanical viscosity increasing agents

In an exemplary embodiment of the invention, the cement includes particles characterized by a large surface which do not participate in the polymerization reaction. The 15 large surface area particles can impart added viscosity to the cement mixture independent of polymerization. Optionally, the added viscosity comes from friction of particles against one another in the cement.

Examples of materials which do not participate in the polymerization reaction but increase viscosity include, but are not limited to Zirconium, hardened acrylic polymer, barium 20 sulfate and bone.

Optionally, materials which do not participate in the polymerization reaction but increase viscosity can at least partially substitute for high MW polymers in influencing a viscosity profile.

Desired Polymerization Reaction Kinetics

25 In an exemplary embodiment of the invention, mixture of polymer and monomer produces a high viscosity mixture with substantially no intervening liquid phase within 180, optionally within 120, optionally within 100, optionally within 60, optionally within 30, optionally within 15 seconds or greater or intermediate times from onset of mixing.

In an exemplary embodiment of the invention, once a high viscosity is achieved, the 30 viscosity remains stable for 5 minutes, optionally 8 minutes, optionally 10 minutes or lesser or intermediate or greater times. Optionally, stable viscosity indicates a change of 10% or less in two minutes and/or a change of 20% or less in 8 minutes. The time during which viscosity is stable provides a working window for performance of a medical procedure.

These desired reaction kinetics can be achieved by adjusting one or more of average polymer MW, polymer MW distribution, polymer to monomer ratio and polymer bead size and/or size distribution.

General considerations

5 In an exemplary embodiment of the invention, a powdered polymer component and a liquid monomer component are provided as a kit. Optionally, the kit includes instructions for use. Optionally, the instructions for use specify different proportions of powder and liquid for different desired polymerization reaction kinetics.

In an exemplary embodiment of the invention, a bone cement kit including at least two,
10 optionally three or more separately packaged sub-populations of beads and a monomer liquid is provided. Optionally, the kit includes a table which provides formulations based on combinations of different amounts of bead sub-populations and monomer to achieve desired properties.

It is common practice in formulation of acrylic polymer cements to include an initiator
15 (e.g. benzoyl peroxide; BPO) in the powdered polymer component and/or a chemical activator (e.g. DMPT) into the liquid monomer component. These components can optionally be added to formulations according to exemplary embodiments of the invention without detracting from the desired properties of the cement.

20 Optionally, an easily oxidized molecule (e.g. hydroquinone) is added to the liquid component to prevent spontaneous polymerization during storage (stabilizer). The hydroquinone can be oxidized during storage.

Optionally, cement may be rendered radio-opaque, for example by adding a radio-opaque material such as barium sulfate and/or zirconium compounds and/or bone (e.g. chips or powder) to the powder and/or liquid component.

25 While the above description has focused on the spine, other tissue can be treated as well, for example, compacted tibia plate and other bones with compression fractures and for fixation of implants, for example, hip implants or other bone implants that loosened, or during implantation. Optionally, for tightening an existing implant, a small hole is drilled to a location where there is a void in the bone and material is extruded into the void.

30 It should be noted that while use of the disclosed material as bone cement is described, non-bone tissue may optionally be treated. For example, cartilage or soft tissue in need of tightening may be injected with a high viscosity polymeric mixture. Optionally, the delivered material includes an encapsulated pharmaceutical and is used as a matrix to slowly release the

pharmaceutical over time. Optionally, this is used as a means to provide anti-arthritis drugs to a joint, by forming a void and implanting an eluting material near the joint.

It should be noted that while use of PMMA has been described, a wide variety of materials can be suitable for use in formulating cements with viscosity characteristics as described above. Optionally, other polymers could be employed by considering polymer molecular weight (average and/or distribution) and/or bead size as described above. Optionally, at least some of the beads include styrene. In an exemplary embodiment of the invention, styrene is added to MMA beads in a volumetric ratio of 5-25%. Optionally, addition of styrene increases creep resistance.

According to various embodiments of the invention, a bone cement according to the invention is injected into a bone void as a preventive therapy and/or as a treatment for a fracture, deformity, deficiency or other abnormality. Optionally, the bone is a vertebral body and/or a long bone. In an exemplary embodiment of the invention, the cement is inserted into the medullary canal of a long bone. Optionally, the cement is molded into a rod prior to or during placement into the bone. In an exemplary embodiment of the invention, the rod serves as an intra-medular nail.

Exemplary Characterization Tools

Molecular weight and polydispersity can be analyzed, for example by Gel permeation chromatography(GPC) system (e.g. Waters 1515 isocratic HPLC pump with a Waters 2410 refractive-index detector and a Rheodyne (Coatati, CA) injection valve with a 20- μ L loop (Waters Ma)). Elution of samples with CHCl₃ through a linear Ultrastyragel column (Waters; 500- \AA pore size) at a flow rate of 1 ml/min provides satisfactory results.

It will be appreciated that various tradeoffs may be desirable, for example, between available injection force, viscosity, degree of resistance and forces that can be withstood (e.g. by bone or injection tools). In addition, a multiplicity of various features, both of method and of cement formulation have been described. It should be appreciated that different features may be combined in different ways. In particular, not all the features shown above in a particular embodiment are necessary in every similar exemplary embodiment of the invention. Further, combinations of the above features are also considered to be within the scope of some exemplary embodiments of the invention. In addition, some of the features of the invention described herein may be adapted for use with prior art devices, in accordance with other exemplary embodiments of the invention.

Section headers are provided only to assist in navigating the application and should not be construed as necessarily limiting the contents described in a certain section, to that section.

Measurements are provided to serve only as exemplary measurements for particular cases, the exact measurements applied will vary depending on the application. When used in the following claims, the terms "comprises", "comprising", "includes", "including" or the like means "including but not limited to".

5 It will be appreciated by a person skilled in the art that the present invention is not limited by what has thus far been described. Rather, the scope of the present invention is limited only by the following claims.

CLAIMS

1. A bone cement comprising an acrylic polymer mixture, the cement characterized in that it achieves a viscosity of at least 500 Pascal-second within 180 seconds following initiation of mixing of a monomer component and a polymer component and characterized by sufficient biocompatibility to permit in-vivo use.
5
2. A bone cement according to claim 1, wherein the viscosity of the mixture remains between 500 and 2000 Pascal-second for a working window of at least 5 minutes after the initial period.
10
3. A bone cement according to claim 2, wherein the working window is at least 8 minutes long.
15
4. A bone cement according to any of the preceding claims, wherein the mixture includes PMMA.
20
5. A bone cement according to any of the preceding claims, wherein the mixture includes Barium Sulfate.
25
6. A bone cement according to claim 4 or 5, wherein the PMMA is provided as a PMMA/styrene copolymer.
30
7. A bone cement according to claim 4, 5 or 6, wherein the PMMA is provided as a population of beads divided into at least two sub-populations, each sub-population characterized by an average molecular weight.
25
8. A bone cement according to claim 7, wherein a largest sub-population of PMMA beads is characterized by an MW of 150,000 Dalton to 300,000 Dalton.
30
9. A bone cement according to claim 7 or 8, wherein a largest sub-population of PMMA beads includes 90-98% (w/w) of the beads.

10. A bone cement according to claim 7, 8 or 9, wherein a high molecular weight sub-population of PMMA beads is characterized by an average MW of at least 3,000,000 Dalton.

11. A bone cement according to any one of claims 7-10, wherein a high molecular weight
5 sub-population of PMMA beads includes 2 to 3% (w/w) of the beads.

12. A bone cement according to any one of claims 7-11, wherein a low molecular weight sub-population of PMMA beads is characterized by an average MW of less than 15,000 Dalton.

10

13. A bone cement according to any one of claims 7-12, wherein a low molecular weight sub-population of PMMA beads includes 0.75 to 1.5 % (W/W) of the beads.

15

14. A bone cement according to any one of claims 4-13, wherein the PMMA is provided as a population of beads divided into at least two sub-populations, each sub-population characterized by an average bead diameter.

20

15. A bone cement according to claim 14, wherein at least one bead sub-population of characterized by an average diameter is further divided into at least two sub-sub-populations, each sub-sub-population characterized by an average molecular weight.

16. A bone cement according to claim 14, wherein the PMMA is provided as a population of beads divided into at least three sub-populations, each sub-population characterized by an average bead diameter.

25

17. A bone cement according to any of the preceding claims, further comprising processed bone and/or synthetic bone.

30

18. A bone cement according any of the preceding claims, characterized in that the cement achieves a viscosity of at least 500 Pascal-second when 100% of a polymer component is wetted by a monomer component.

19. A bone cement according any of the preceding claims, wherein the viscosity is at least 800 Pascal-second.

20. A bone cement according any of the preceding claims, wherein the viscosity is at least 1500 Pascal-second.

5 21. A bone cement according any of the preceding claims, wherein the viscosity is achieved within 2 minutes.

22. A bone cement according any of the preceding claims, wherein the viscosity is achieved within 1 minute.

10

23. A bone cement according any of the preceding claims, wherein the viscosity is achieved within 45 seconds.

24. A bone cement comprising:

15

a polymer component; and

a monomer component;

wherein contacting the polymer component and the monomer component produces a mixture which attains a viscosity greater than 200 Pascal-second within 1 minute from onset of mixing and remains below 2000 Pascal-second until at least 6 minutes from onset of mixing.

20

25. A bone cement according to claim 24, wherein the polymer component comprises an acrylic polymer.

26. A particulate mixture formulated for preparation of a bone cement, the mixture comprising:

25

(a) 60 to 80% polymer beads comprising a main sub-population characterized by an MW of 150,000 Dalton to 300,000 Dalton and a high molecular weight sub-population characterized by an MW of 3,000,000 Dalton to 4,000,000 Dalton; and

(b) 20 to 40% of a material which is non-transparent with respect to X-ray.

30

27. A mixture according to claim 26, wherein the polymer beads comprise a third subpopulation characterized by an MW of 10,000 Dalton to 15,000 Dalton.

28. A method of making a polymeric bone cement, the method comprising:

- (a) defining a viscosity profile including a rapid transition to a working window characterized by a high viscosity;
- (b) selecting a polymer component and a monomer component to produce a cement conforming to the viscosity profile; and

5 (c) mixing the polymer component and a monomer component to produce a cement which conforms to the viscosity profile.

1/4

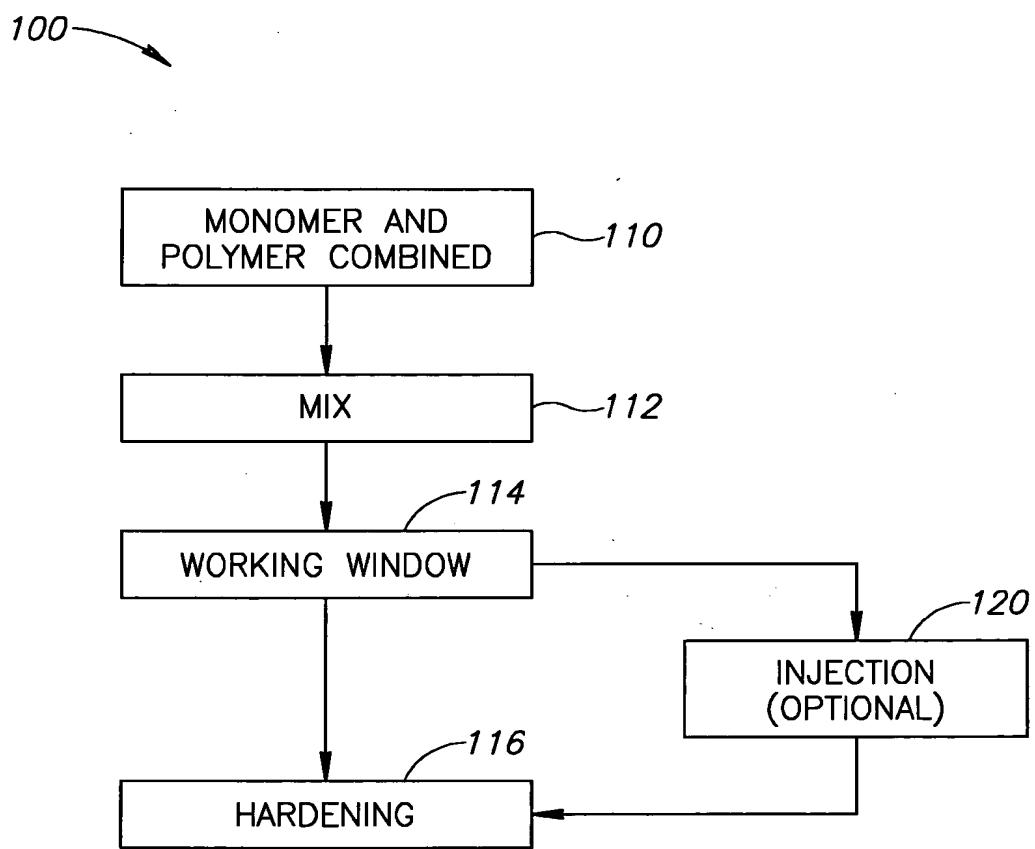


FIG.1

2/4

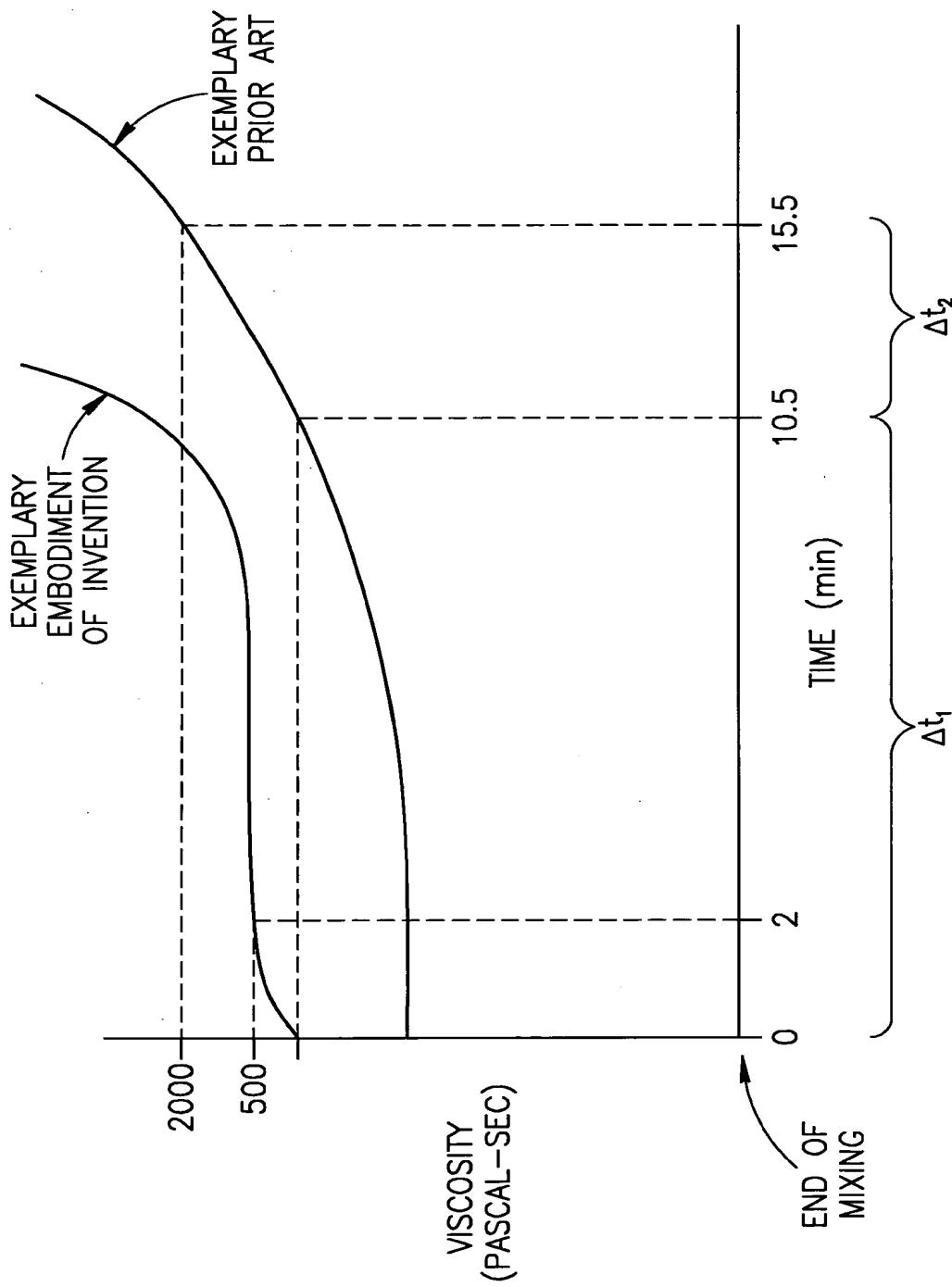
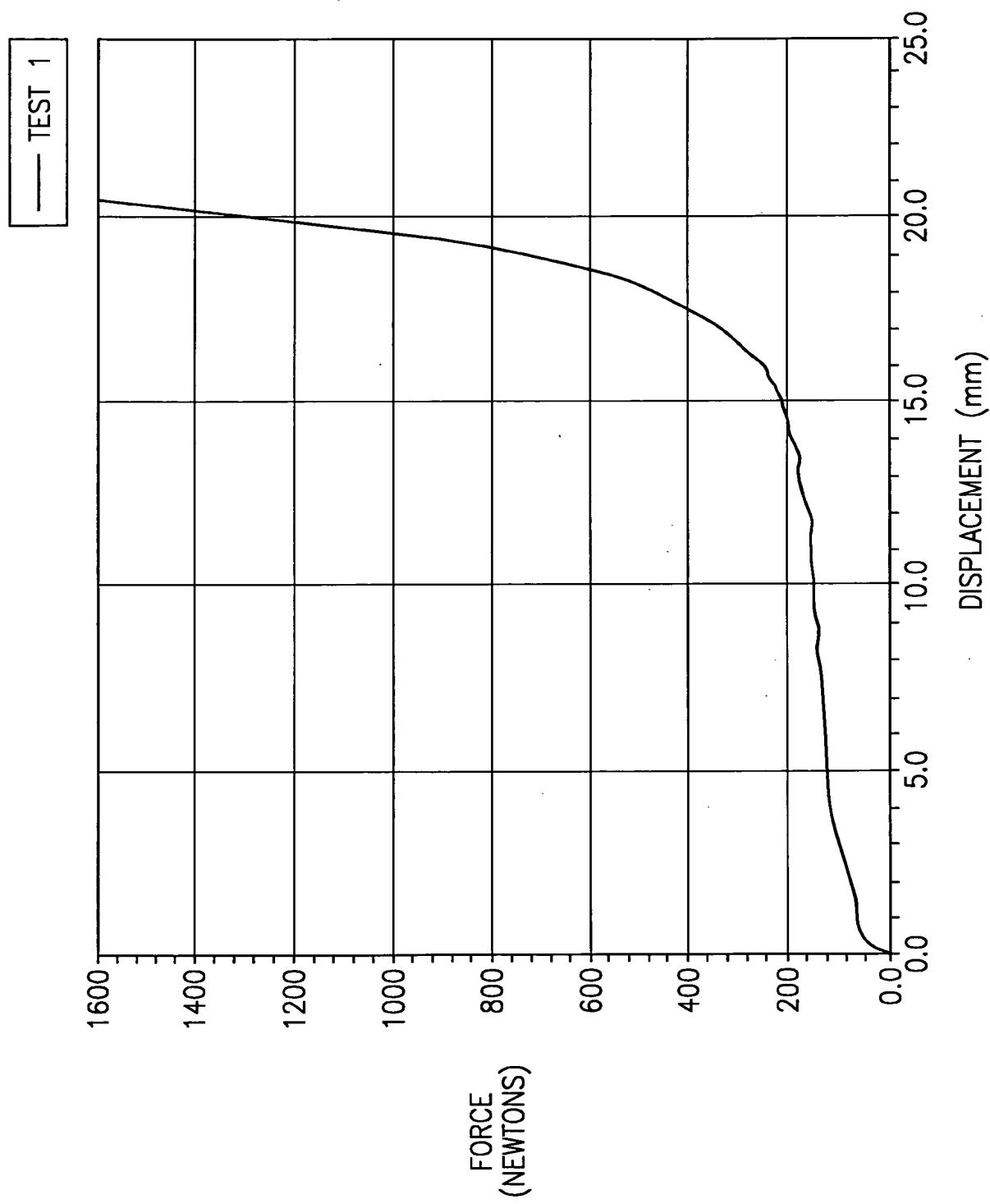


FIG. 2

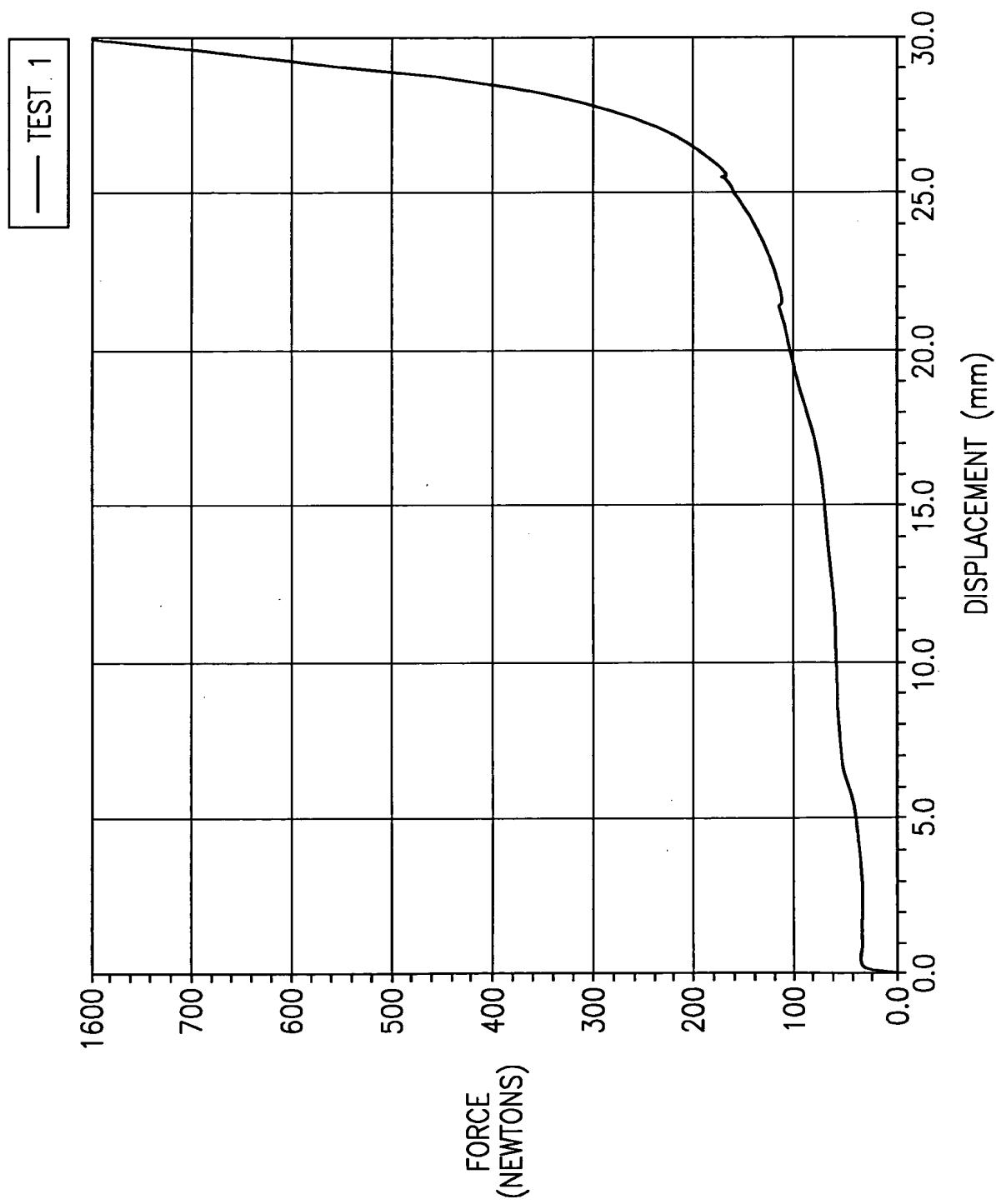
3/4

FIG. 3



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FIG.4



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(54) Title: BONE CEMENT AND METHODS OF USE THEREOF

(57) Abstract: A bone cement comprising an acrylic polymer mixture. The cement is characterized in that it achieves a viscosity of at least 500 Pascal-second within 180 seconds following initiation of mixing of a monomer component and a polymer component and characterized by sufficient biocompatibility to permit in-vivo use.

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEWIS GLADIUS: "Properties of acrylic bone cement: State of the art review" JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, vol. 38, no. 2, 1997, pages 155-182, XP002432739 ISSN: 0021-9304 page 158, paragraph VISCOSITY; table II -----	1-5, 18-23
A	LEWIS GLADIUS: "Toward standardization of methods of determination of fracture properties of acrylic bone cement and statistical analysis of test results" JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, vol. 53, no. 6, 2000, pages 748-768, XP002432740 ISSN: 0021-9304 the whole document -----	1-23 -/-

 Further documents are listed in the continuation of Box C. See patent family annex.

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- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

10 May 2007

02/10/2007

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FISCHER, J

INTERNATIONAL SEARCH REPORT

International application No PCT/IB2006/052612

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/019810 A (BIOMET INC [US]; SMITH DANIEL B [US]; EPPLEY BARRY L [US]) 11 March 2004 (2004-03-11) the whole document -----	1, 4-16
A	WO 99/18894 A1 (PARALLAX MEDICAL INC [US]; PREISSMAN HOWARD [US]) 22 April 1999 (1999-04-22) examples 1,2 -----	1-5
A	FR 2 638 972 A1 (OSTEAL MEDICAL LABORATOIRES [FR]) 18 May 1990 (1990-05-18) the whole document -----	1-18
A	WO 2004/071543 A (SYNTHES AG [CH]; SYNTHES USA [US]; BISIG ADRIAN [CH]; BOHNER MARC [CH]) 26 August 2004 (2004-08-26) the whole document -----	1-18
A	EP 0 177 781 A1 (DRAENERT KLAUS) 16 April 1986 (1986-04-16) the whole document -----	1-18

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/IB2006/052612**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-23, 25

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-23,25

A bone cement comprising an acrylic polymer mixture, the cement characterized in that it achieves a viscosity of at least 500 Pascal-second within 180 seconds following initiation of mixing of a monomer component and a polymer component and characterized by sufficient biocompatibility to permit in-vivo use.

2. claim: 24

A bone cement comprising: a polymer component; and a monomer component; wherein contacting the polymer component and the monomer component produces a mixture which attains a viscosity greater than 200 Pascal-second within 1 minute from onset of mixing and remains below 2000 Pascal-second until at least 6 minutes from onset of mixing.

3. claims: 26-27

A particulate mixture formulated for preparation of a bone cement, the mixture comprising:
(a) 60 to 80% polymer beads comprising a main sub-population characterized by an MW of 150,000 Dalton to 300,000 Dalton and a high molecular weight sub-population characterized by an MW of 3,000,000 Dalton to 4,000,000 Dalton; and
(b) 20 to 40% of a material which is non-transparent with respect to X-ray..

4. claim: 28

A method of making a polymeric bone cement, the method comprising:
(a) defining a viscosity profile including a rapid transition to a working window characterized by a high viscosity;
(b) selecting a polymer component and a monomer component to produce a cement conforming to the viscosity profile; and
(c) mixing the polymer component and a monomer component to produce a cement which conforms to the viscosity profile.

INTERNATIONAL SEARCH REPORT

Information on patent family members

 International application No
PCT/IB2006/052612

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 2004019810	A	11-03-2004	AU US	2003262797 A1 2004044096 A1		19-03-2004 04-03-2004
WO 9918894	A1	22-04-1999	AU US US	1081999 A 6231615 B1 6309420 B1		03-05-1999 15-05-2001 30-10-2001
FR 2638972	A1	18-05-1990		NONE		
WO 2004071543	A	26-08-2004	AU BR CA EP JP	2003203316 A1 0317809 A 2516113 A1 1592463 A1 2006513760 T		06-09-2004 29-11-2005 26-08-2004 09-11-2005 27-04-2006
EP 0177781	A1	16-04-1986	JP JP JP	1875320 C 5088147 B 61068053 A		07-10-1994 21-12-1993 08-04-1986